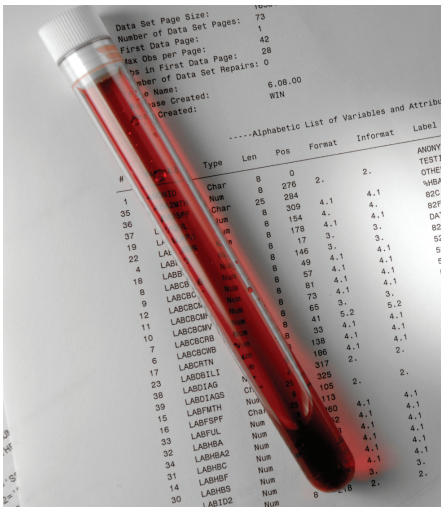

[ORIGINAL RESEARCH]

Are Clozapine Blood Dyscrasias Associated with Concomitant Medications?

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Innov Clin Neurosci. 2011;8(4):35–41

FUNDING: There was no funding for the development and writing of this article.

FINANCIAL DISCLOSURES: The authors list no conflicts of interest relevant to the content of this article.

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KEY WORDS: Clozapine, concomitant risks, agranulocytosis

ABSTRACT

Clozapine is an atypical antipsychotic agent used for refractory schizophrenia. It has a relatively low affinity for D2 receptors and thus is associated with a lower incidence of extrapyramidal side effects when compared with typical antipsychotics. Clozapine as monotherapy can induce a rare, but serious, blood dyscrasia called agranulocytosis; however, some concomitant medications may contribute to the risk. Examples of these medications are mood-stabilizing antiepileptic drugs, such as carbamazepine, and sulfonamide antibiotics, such as sulfamethoxazole. There were no studies at the writing of this article examining the effect of concomitant medications on clozapine blood dyscrasias, and few published reports describing enhanced bone marrow suppression in those taking clozapine. The primary objective of this study was to evaluate the effect of concomitant medications used in a state psychiatric hospital on clozapine-induced blood dyscrasias. This was a retrospective record review of adverse drug reactions reported at an adult inpatient state psychiatric center. The records for a pilot sample of 26 patients with reported clozapine-related adverse drug reactions between January 1, 2007, and June 30, 2009, were reviewed. Fundamental to this study were reported adverse drug reactions defined as 1) substantial drops in white blood cell or absolute neutrophil count (a substantial drop in white blood cell is >3,000 or absolute neutrophil count is >1,500 over a 3-week period); 2) mild leukopenia/granulocytopenia; and 3) moderate-severe leukopenia/granulocytopenia. Concomitant medications were examined for contributions to an increased potential for clozapine-induced blood dyscrasias. Other data collected included demographic information (age, gender, ethnicity), medical and psychiatric diagnoses, dose and duration of medications, and changes in medications. Medications that had a statistically significant impact on the incidence of clozapine-induced blood dyscrasias are reported in this article, as well as the possible duration of medication use prior to induction of an adverse drug reaction.

INTRODUCTION

Clozapine was the first atypical (second generation) antipsychotic introduced in the United States in 1990. The superior efficacy of clozapine compared to other antipsychotics has been established. It is also well documented that clozapine can induce a rare but life-threatening blood dyscrasia called agranulocytosis in approximately 1.3 percent of patients during the first year of clozapine therapy.[1] *Agranulocytosis* is defined as an absolute neutrophil count (ANC) less than 500/mm^3. The specific mechanism of how clozapine induces agranulocytosis is still unknown. Hypotheses currently include an immune process and induction of neutrophil apoptosis, although neither has been proven as the pathophysiology behind agranulocytosis. Clozapine is contraindicated in combination with other medications with their own potential to cause agranulocytosis (i.e., carbamazepine and anticancer agents) because of the possibility of a synergistic pharmacodynamic interaction. Because this interaction has not been systematically studied for those medications currently approved for coadministration with clozapine, there may be other medications used in combination with clozapine that also have the potential to act synergistically, leading to agranulocytosis.[2]

The objective of this study was to determine if a relationship existed between concomitant medications and clozapine-related white blood cell (WBC)/ANC events.

OVERVIEW OF THE LITERATURE

Agranulocytosis is a sudden condition involving a drop in the concentration of granulocytes—major contributors to white blood cell volume. Agranulocytosis is characterized by leukopenia and neutropenia, involving the neutrophils, basophils, and eosinophils. Agranulocytosis usually appears 21 to 28 days after starting clozapine treatment, can last up to about three months, and can be clinically defined as a severe neutropenia with neutrophils below 500 cells per microliter.[1,3] This immunodeficiency condition is dangerous and can become life-threatening due to high risk of infection. To ensure appropriate monitoring to prevent agranulocytosis, the clozapine manufacturers conducted a risk analysis based on the data collected by the Clozapine Registry for all patients enrolled in the United States. The incidence rates of agranulocytosis (based on the weekly monitoring schedule) rose steeply during the first two months of therapy, peaking in the third month, and while the incidence declines even further after the sixth month of continuous therapy, the risk never reaches zero.[2,4,5]

Clozapine should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. Though the mechanism of clozapine-induced agranulocytosis is unknown, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.[1] Carbamazepine is an example of a drug that is well known for potential bone marrow suppression; however, even antidepressants include a number of agents found to cause agranulocytosis. Recent data report that schizophrenia affects 1 to 2 percent of the adult population in the United States. Patients with schizophrenia have comordbid depression 25 percent of the time.[3] Some medications, without published case reports of agranulocytosis, may be less likely to be implicated as potential confounders when coadministered with clozapine. Clozapine therapy is most effective when given without interruption; it is, therefore, vital that prevention of therapeutic interruption be a clinical priority. Prevention of temporary interruptions when moderate leukopenic episodes occur, or permanent nonrechallengable interruptions when agranulocytosis occurs, is more likely when more precise and clinically relevant information about concomitant medication is available. Clozapine therapy could be more successful if prescribing clinicians had more information on what combinations of medications to avoid and knowledge of all medications (both prescription and nonprescription) being prescribed by others and taken by the patient on clozapine.

Some medication classes less likely to be considered problematic are general medical medications and psychiatric agents used for multiple indications, including mood stabilizers and antidepressant medications. Tricyclic antidepressants (TCAs) as a class may cause agranulocytosis; this is considered a rare side effect of the class. TCA is one of the older classes of antidepressants, with imipramine as the first (coming to market in 1959). Several other medications, such as amitriptyline, nortriptyline, desipramine, protriptyline, and doxepin, were developed shortly after and have few published case reports of agranulocytosis. As of 1999, after 40 years of imipramine on the market, only 10 cases of agranulocytosis secondary to TCA use have been reported in the literature.[4] The newest TCA, clomipramine, has agranulocytosis reported as a side effect as well as all the other drugs in the class. Heterocyclic antidepressants—mirtazapine and amoxapine—have also been associated with agranulocytosis. Mirtazapine has an incidence of one out of 1,000 patients.[5]

Mood stabilizers, also known as antimanic agents, have been used in psychiatry to treat disorders, such as bipolar disorder, bipolar depression, mania, and borderline personality disorder. The use of anticonvulsants as alternatives or additions to lithium therapy for mood disorders, such as bipolar disorder, has become more widely applied. Following the use of electroconvulsive therapy (ECT) and lithium and augmentation strategies

with antidepressants, neuroleptics became the gold standard for treatment of bipolar illness. Lithium was touted as widely effective in the middle of the 20th century. However, some patients, such as those experiencing dysphoric mania (rapid cycling) were noted to respond less often to lithium.[5] Post's studies in 1998 were on largely uncontrolled populations but were highly suggestive of a psychotropic response. This provided the ground work to explore related agents that might be more efficacious for mood disorders.[5] The term *mood stabilizer* describes an effect, not a mechanism, which came to be used after it was discovered that certain anticonvulsants appeared to be effective in treating some psychiatric disorders.[5] Examples of anticonvulsants found to be effective as mood stabilizers include carbamazepine, valproic acid, lamotrigine, and topiramate (non-United States Food and Drug Administration [FDA] approved off-label use).

A review of the literature revealed a variety of case reports articulating the range of adverse drug reactions. Relevant details of these case reports are included here to demonstrate outcomes where agranulocytosis has been documented with concomitant medications. We cite specific examples of issues with concomitant use, a strong and compelling reason for clinical practitioners to consider with this population.

CASE REPORT AND CONCOMITANT USE STUDIES

This section presents one concomitant use case and studies examining the medical records of subjects taking clozapine as well as concomitant compounds. These are illustrative of the authors' main focus. The next section (Other Reports/Evidence) demonstrates additional clinical data vital to treating this population in a real-world manner to maximize the safety and efficacy of clozapine.

The case study involved a 27-year-old man admitted for depressive mood and auditory hallucinations.[6] The patient had been taking risperidone for six years for bipolar I disorder prior to admission. His admission complete blood count (CBC) revealed a WBC and ANC of 12,670 cell/mm^3 and 9,541 cell/mm^3, respectively. The patient was started on lamotrigine 25mg/day and this was increased to 100mg/day by Day 18. On Day 20, 12.5mg of clozapine was added, and at this point WBC count was 6,510 and ANC was 3,431 cell/mm^3. On Day 29 (29 days after lamotrigine initiation and 9 days after clozapine initiation), the CBC revealed an ANC of 348 cell/mm^3 with agranulocytosis. At this point, the patient was concurrently on 4mg of risperidone and 175mg of clozapine. The lamotrigine was immediately discontinued and on Day 3 after discontinuation the patient's ANC increased to 2,367 cell/mm^3. Risperidone was then also discontinued and the clozapine was increased to 225mg, with no further hematologic abnormalities. Because both the lamotrigine and risperidone were discontinued, it is difficult to detect the separate contribution of these two compounds to the agranulocytosis; however, the clozapine was not the causative agent.

This case report suggests that the increased titration may be more impactful in causing agranulocytosis than the dosage itself. The fast recovery of agranulocytosis is not typically seen with clozapine, suggesting that the lamotrigine-induced agranulocytosis may be caused by a different mechanism.[7] Lamotrigine undergoes glucuronidation in the liver via the uridine diphosphate glucuronyltransferase (UGT) hepatic enzyme system. There are no clearly defined drug interactions with clozapine, as this drug is primarily metabolized by oxidative hepatic metabolism, including but not limited to the CYP 1A2 enzymatic pathway. However, there is one report[8] that describes an interaction between lamotrigine and clozapine that documents a three-fold increase in clozapine concentration in a patient after lamotrigine was added to the medication regimen. The patient experienced sedation and dizziness that were clinically significant, and measurement of clozapine plasma concentrations during the time of the interaction and after lamotrigine was discontinued indicated a probable interaction, although the mechanism of the interaction could not be determined.[8] This interaction may play a role in the rapid improvement from agranuloctyosis and why it was more significant before the lamotrigine was discontinued.

Imbarlina et al[9] retrospectively reviewed the medical data from 225 charts of patients receiving clozapine. The hematological data were collected over a three-month period. Chi-square contingency statistics were used to detect differences between groups that had or had not experienced neutropenia. Leukopenia was defined by less than 3,000 leukocytes per cubic meter and agranulocytosis was defined as less than 500 granulocytes per cubic meter in the study.[9] The patients' ages ranged from 18 to 75 years old. There were 150 male and 75 female patients. Of the 13 patients who received valproic acid in conjunction with clozapine, 23 percent developed neutropenia. Two percent of patients on valproic acid without clozapine developed neutropenia, and none of the patients on clozapine monotherapy in the study developed neutropenia. The study found that the combination of valproic acid and clozapine was associated with a greater risk for neutropenia than with clozapine as monotherapy.

Stubner et al[10] conducted a retrospective study from 1993 to 2000 with 122,562 patients from 35 psychiatric institutions. Researchers documented the cases and frequencies of different blood dyscrasias induced by anticonvulsants, antidepressants, neuroleptics, TCAs, selective serotonin reuptake inhibitors (SSRIs), and clozapine. A psychiatric drug safety program used for assessing the adverse drug reactions

TABLE 1. Categories of medications examined for blood dyscrasia impact in combination with clozapine

Antianxiety
Antibiotics
Antidepressants
Antihypertensive
Antipsychotics, atypical
Antihyperlipidemics
Antipsychotics, typical
Antiviral
Blood thinner
Benign prostatic hyperplasia
Cardioprotection
Cognitive impairment
Constipation
Cough
Decongestant
Diabetes
Gout
Incontinence
Mood stabilizers
Nicotine replacement therapy
Osteoporosis
Pain
Respiratory
Seizures
Sickle cell anemia
Side effect medication
Sleep
Stomach
Supplements
Thyroid
Topicals
Vaccinations
Wake promoting

in Stubner's study is called the AMSP (Arzneimittelsicherheit in der Psychiatry).[12] The individual events were classified according to the probability of the causal relationship of administration of the drug and the observed adverse event. These were recorded on a 0-to-4 scale (0=Possible, 1=Probable, 2=Definite, 3=Relationship Assumed, or 4=Nonassessable). Of the 15,414 patients exposed to clozapine, 0.18 percent developed severe neutropenia (i.e., agranulocytosis). Of 13,525 patients taking carbamazepine, 0.14 percent developed agranulocytosis. Olanzapine and valproate had the next highest frequency of agranulocytosis with 0.05 percent, and doxepin had the highest incidence of agranulocytosis of the antidepressants monitored in the study at 0.04 percent. TCAs as a class were calculated to be 0.02 percent.[10]

OTHER REPORTS/ EVIDENCE

This case report of a 29-year-old woman[11] described her 2009 admission for severe abdominal pain, nausea, and insomnia. Her WBC was 6,000 and ANC was 4.55 cells/µL. Mirtazapine 15mg/day was initiated 24 hours after the blood work was completed. After the first dose of mirtazapine, her WBC was 3,000, and the ANC decreased to 2.18. After two doses, her ANC fell to 0.92. Her ANC further fell to 0.81 after her third dose and to 0.53 after her fourth dose. Her WBC and hemoglobin values fluctuated but remained within acceptable range between the first and fourth dose. Her ANC increased to 0.63 one day after discontinuation of mirtazapine. The association between the administration of mirtazapine and the temporary lowering of the neutrophil count strongly suggest that the neutropenia was related to mirtazapine.[11]

Yong Min Ahn et al[6] reported 13 cases of agranulocytosis believed to be associated with lamotrigine. Excerpts include the case of a 20-year-old man admitted to the psychiatric ward for depressive mood of bipolar I disorder. The WBC and ANC upon admission were 4,400 cell/mm^3 and 2,240 cell/mm^3, respectively. Treatment with lamotrigine 12.5mg/day and amisulpiride was initiated. Lamotrigine was increased to 75mg/day after four weeks and the amisulpiride dose was 200mg/day. Fluoxetine was prescribed at Week 5 and lamotrigine was increased to 100mg/day by Week 6. The WBC and ANC were 2,390 and 574 cell/mm^3, respectively, after 45 days of lamotrigine therapy. Lamotrigine was discontinued while the other drugs were continued. The CBC the following day revealed an ANC of 380 cell/mm^3 with agranulocytosis. Subsequently, 30mcg of granulocyte colony-stimulating factor (G-CSF) and filgrastim were injected. The CBC on Day 6 after discontinuation of lamotrigine showed an ANC of 3,503 cell/mm^3 with a normal WBC.[6] The outcome in this case may be impacted by the G-CSF and filgrastim intervention and must be considered within that clinical framework. All the patients' hematologic abnormalities reported by Yong Min Ahn et al[6] were normal within one week after lamotrigine discontinuation, which corroborates the clinical implications of the case reports.

Weisler et al[13] conducted a randomized, double-blind, placebo-controlled study on the efficacy and safety of carbamazepine as monotherapy for bipolar patients with mixed or manic episodes. The study included 204 patients. Although the study noted that carbamazepine carries a black box warning for agranulocytosis, no patient in this study experienced agranulocytosis or leukopenia.

METHODS

Retrospective chart reviews were conducted (N=26) on inpatients at a state psychiatric inpatient facility for those receiving clozapine and concomitant medications to detect

adverse drug reactions involving blood dyscrasias. See Table 1 for the medication categories examined for their synergistic impact on clozapine's propensity for blood dyscrasias.

RESULTS

This protocol was approved by the New York State Psychiatric Institute Institutional Review Board. This was a retrospective chart review of the sample of 26 psychiatric inpatients taking clozapine with a documented WBC/ANC event within the study time period of January 1, 2007, to June 30, 2009. Adverse events are defined using the monitoring values in the clozapine package insert and were divided into three categories: substantial drops, mild leukopenia/granulocytopenia, and moderate-to-severe leukopenia/granulocytopenia. See Tables 2 and 3 for values and Figure 1 for the proportion of actual ADR events.

Variables used to detect a correlation between concomitant medications and clozapine-induced events were the "Type of Event" and "All Medications Administered for 3 Months Prior to the Event." A Pearson's Correlation Coefficient, with $p<0.05$, was used to determine statistical significance of possible correlations between concomitant medications and WBC/ANC events.

The mood stabilizers in this study included lithium, valproate/divalproex, lamotrigine, topiramate, and oxcarbazepine. The antidepressants considered were three SSRIs (escitalopram, citalopram, sertraline) and one SNRI (duloxetine). The combination of clozapine, anxiolytic, and antidepressant medications creating an ANC/WBC event was statistically significant ($p<0.003$). The combination of clozapine, anxiolytic, and mood stabilizer medications creating an ANC/WBC event was also statistically significant ($p<0.033$). Because these medications have been documented to induce agranulocytosis individually, these results are expected. However, antibiotics were anecdotally suspected to decrease WBC and ANC, and our results demonstrated no significant correlation between taking an antibiotic and an event occurring within three months.

DISCUSSION

This pilot study demonstrated that the combination of clozapine, anxiolytic, and antidepressant medications had a statistically significant level of ANC/WBC event ($p<0.003$ at probability level 0.05). The combination of clozapine, anxiolytic, and mood stabilizer medications also had a statistically significant level of ANC/ WBC event ($p<0.033$ at probability level 0.05). Because these medications have been documented to induce agranulocytosis individually, these results were expected. The results regarding antibiotics may have been due to the small size of the sample, as well as the overall health of the sample during data collection.

Documented substantial drops may be due to resolution of an infection with or without an antibiotic, and therefore may not be related to clozapine. It has been clinical practice in the facility to allow the patient's immune system time to respond with natural recovery to a low-level infection as opposed to prescribing antibiotics.

The concurrent use of clozapine with other agents having a well-known ability to cause agranulocytosis is contraindicated. Although the incidence is low, carbamazepine has been associated with agranulocytosis and aplastic anemia. Per the manufacturer's recommendations, the co-administration of the two should be avoided.[1] Some clinicians still choose to place patients on clozapine and carbamazepine (e.g., patients who have schizophrenia and seizure disorders). Clozapine and carbamazepine both cause neutropenia and agranulocytosis.[7,15,16] The concomitant interaction is well documented in the literature.

TABLE 2. Clozapine monitoring

Initiating Treatment
WBC>3,500/mm^3
ANC>2,000/mm^3
Substantial drop: Cumulative within 3 weeks
WBC>3000/mm^3
ANC>1500/mm^3
Leukopenia and granulocytopenia
Mild WBC: 3,000–3,499/mm^3 ANC: 1,500–1,999/mm^3
Moderate to Severe WBC: 2,000–2,999/mm^3 ANC: 1,000–1,499/mm^3

KEY: WBC=white blood cell; ANC=absolute neutrophil count

However, the discontinuation of carbamazepine in a patient who is also on clozapine can cause clozapine levels to rise, also increasing the chance for additional adverse drug events.

Much of the published research involving antidepressants and agranulocytosis were case reports. In large retrospective trials with a large number of patients, the incidence of agranulocytosis was miniscule, with less than 0.01 percent in most studies. Randomized, controlled studies for efficacy of mood stabilizers and antidepressants were not likely to detect the side effect of agranulocytosis. The study sample size was not large enough because the side effect is so rare in these drug classes. Data of agranulocytosis from these classes came largely from retrospective studies looking at sample sizes over 100,000 patients or case reports of specific events. The literature seems to support the notion that agranulocytosis is very uncommon among the antidepressant class, less than 0.01 percent overall.[11] Of the antidepressants involved in cases of agranulocytosis and neutropenia in the literature, heterocyclics, such as

TABLE 3. Concomitant medications and combinations

MEDICATIONS	PEARSON CORRELATION	PROBABILITY
FGAs		
with SGAs	0.054	0.792
with antidepressants	-0.13	0.526
with mood stabilizers	0.14	0.494
with anxiolytics	0.307	0.127
SGAs		
with antidepressants	0.319	0.112
with mood stabilizers	0.202	0.323
with anxiolytics	0.149	0.468
Antidepressants		
with SGAs	0.319	0.112
with mood stabilizers	-0.049	0.812
with anxiolytics	0.554	0.003*
Mood stabilizers		
with SGAs	0.202	0.323
with antidepressants	-0.049	0.812
with anxiolytics	0.418	0.033*

* Statistical significance at 0.05

KEY: FGA=first-generation antipsychotic; SGA=second-generation antipsychotic

mirtazapine and amoxapine, and TCAs, such as doxepin and imipramine, were identified. The literature does not support SSRIs or SNRIs causing agranulocytosis.

Of the mood stabilizers, carbamazepine is widely known to cause agranulocytosis in monotherapy.[6] Carbamazepine has been shown to cause a statistically significant decrease in WBC. Serious cases of agranulocytosis warrant discontinuation of carbamazepine and prophylactic antibiotics to prevent infection.[15] Patients who are at risk for these conditions may continue therapy while being closely monitored. Research shows that valproic acid is the most documented of the mood stabilizer class to cause or increase the chance of agranulocytosis while used adjunctively with clozapine. The mechanism of increased risk of neutropenia with valproic acid and clozapine is not fully understood. It may be related to the ability of valproic acid to increase the unbound concentration of clozapine.[6] Lamotrigine also has documented cases of agranulocytosis.[12]

Further research is needed to ascertain which antidepressants and mood stabilizers cause agranulocytosis and which increase the chance of agranulocytosis when given with clozapine. However, current data support that the chance of agranulocytosis is greater with clozapine when given concurrently with agents of the mood stabilizer class, specifically carbamazepine or valproic acid as adjunctive therapy.

As a naturalistic, retrospective study, this study examined the real-world application of clozapine therapy with a group of state psychiatric center patients. As such, one of this study's limitations was the lack of a control group. If the concomitant medications for those patients on clozapine who did not experience an event were examined, this could have provided the authors better insight into which medications may put patients at higher risk for agranulocytosis. Future research including a control group is planned.

The results of this study suggest that use of combinations of anxiolytics, mood stabilizers, and antidepressants in patients taking clozapine increase the likelihood of an event associated with ANC/WBC. These combinations can be avoided to reduce the likelihood of an event. Clozapine is an important drug for many individuals suffering from schizophrenia, especially in a state hospital population. Most people taking clozapine have failed many other treatment options, and avoiding a potential adverse drug reaction, such as agranulocytosis, is crucial for these individuals so they can remain on the most effective therapy for their illness. One of the most serious side effects and challenges of clozapine therapy is agranulocytosis, which has been documented as an idiosyncratic

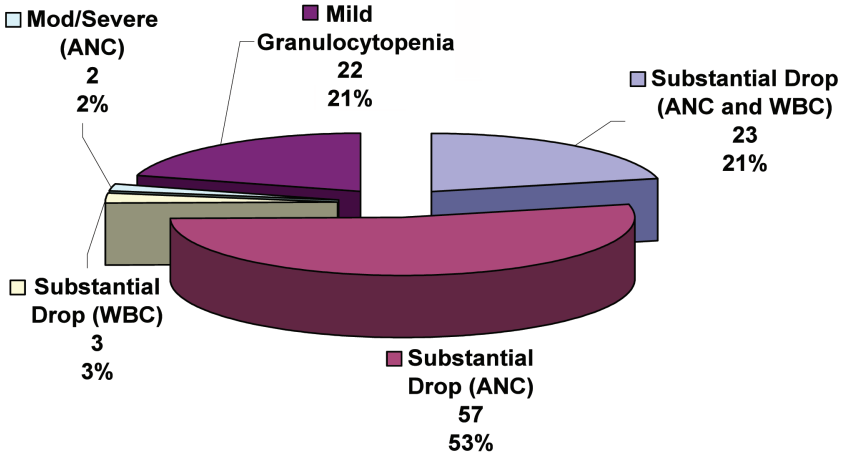

FIGURE 1. Proportion of sample's adverse drug reaction events

reaction occurring with even low doses in the first few weeks of therapy. As it can be asymptomatic, all clinicians must be vigilant during therapy and avoid confounding risks wherever possible.[7]

Further studies with an expanded patient population, a control group, and a specific breakdown of medications (within the class identified as statistically significant for this sample) have the potential to contribute further into this important clinical issue.

ACKNOWLEDGMENT

The authors wish to acknowledge Gail Black Proctor, RPh, and Miranda Cole, PharmD, for their contribution to the data collection and Jathiyah A. Lewis, PharmD candidate, for her contribution to the comprehensive literature review.

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